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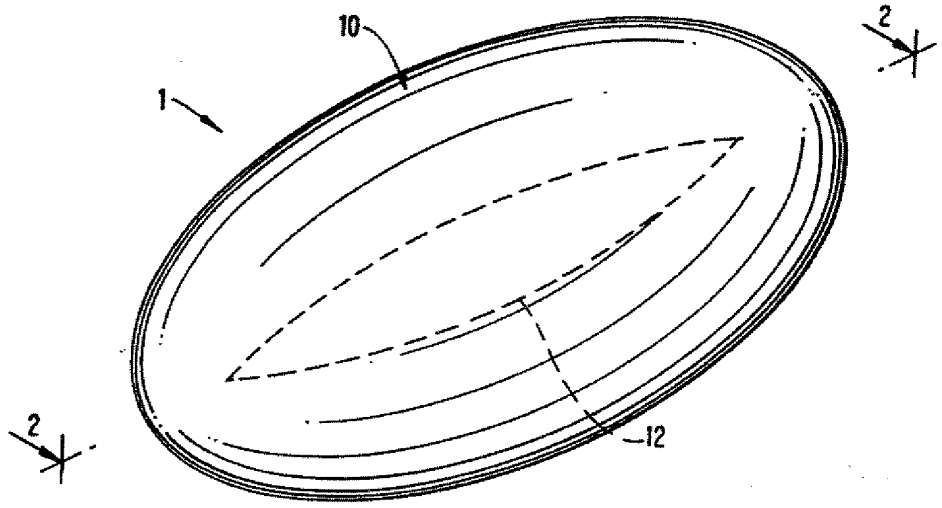

(57) Abstract

An article for controlled release of medication from a dosage form wherein the article comprises a core containing said medication and a coating on the core having a non constant thickness.

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ARTICLE CONTAINING A CORE AND A COATING HAVING A NON CONSTANT THICKNESS

BACKGROUND OF THE INVENTION

This invention relates to articles for the sustained release of pharmaceutical compositions contained therein. More particularly, it relates to articles comprising a core, containing said pharmaceuticals, at least partially coated with a coating of non-uniform thickness and processes for preparing such articles.

Controlled release of a medicine or drug is important for several reasons. In the first place it serves to provide the body with medication over a long time and thereby eliminates the need for ingesting standard dosage forms, e.g., tablets, comprising said medications, at frequent intervals. The treatment of any disease with a medicine requires a fairly constant high blood titre of the medicine. If the medicine is metabolized or otherwise eliminated quickly from the body it would be necessary to swallow an ordinary tablet quite often to maintain the desired blood level.

Some medicines have such a narrow therapeutic ratio that slightly more than is necessary, to achieve a therapeutic effect, will cause adverse toxic symptoms. If an ordinary tablet is taken, the rapid release of its medicament content may cause such a high blood level thereof that undesirable side reactions will occur.

Other medicines are irritating to the alimentary mucosa and their rapid release from ordinary dosage forms may cause damage to the alimentary organs. It is, therefore, desirable that dosage forms release such medications at a very low, preferably zero, initial rate and then at an exponentially increased rate upon reaching the stomach and/or intestine as required.

Dosage forms have been prepared in the past which will control the release of the contained medicine but they have not been entirely satisfactory. Some of them have been expensive to make either because of the expensive ingredients or the complicated apparatus or processes to make them or they have been too large to ingest because of the necessary additives to obtain the delayed release. Other tablets have been unsatisfactory because they have lacked a uniform release time although made in exactly the same way. U.S. Patents 3,538,214 and 4,060,598 refer to a tablet comprising a coating comprising a plastic material, insoluble in gastro-intestinal fluids, and a composition which is removable from the coating upon contact with either the stomach or intestinal fluids to form a dialytic membrane through which the medication slowly diffuses.

United States Patent 4,173,626 refers to a dosage form comprising a capsule containing a mixture comprising pellets of a medication which are uncoated and pellets of said medication coated with a slow dissolving material.

United States Patents 3,119,742 and 3,492,397 refer to dosage forms comprising a mixture of groups of coated pellets of a medicament wherein said coating comprises a slow dissolving material, with each group comprising a constant thickness of coating which differs from that of the other groups. Alternatively, the '742 patent indicates that each group may be coated with coating compositions of differing solubility rates.

The articles of the present invention employ inexpensive formulation materials and achieve controlled release of the medicine. These articles can be made of relatively small size. Furthermore, the total elapsed drug release time can be varied and established by the practice of this invention.

SUMMARY OF THE INVENTION

The present invention provides articles which overcome the above disadvantages. The articles may be so prepared that, by judicious choice of coating material, erosion of the coating in the alimentary canal may be limited to a small, if any, amount of erosion. The major portion of the medication will be released in the gastro-intestinal tract and, depending on the choice of coating material, said release can be limited to the stomach or intestine.

In accordance with the invention, a core, e.g., a tablet, or capsule, containing the drug is made in a conventional manner and to at least a portion of it is applied an erodible coating composition, in a nonuniform thickness, which will slowly be removed from the surface of the core. This slow erosion action will occur because gastro-intestinal fluids will slowly dissolve or disintegrate the coating to reach the drug in the core.

As the core is coated in a nonuniform manner the various portions of the surface of said core are contacted by said gastrointestinal fluids at different times. The core releases its pharmaceutical content at a rate which is proportional to the exposed surface area and concentration of medication in the core. As the erosion of the coating proceeds the exposed surface area of the core increases. During the same time, while the exposed core surface area has been increasing the concentration of the drug, in the core, has been decreasing. The overall effect of increasing exposed core surface area and decreasing drug concentration in the core is to maintain an approximately

constant rate of drug release from the core. In the case of a core exhibiting constant drug release, the increasing exposure of the core of the article causes the drug to be released at an increasing rate.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a perspective view of a first embodiment of the invention.

Figure 2 is a front sectional view of the first embodiment along line 2-2 of Figure 1.

Figure 3 is a side sectional view of the first embodiment along line 3-3 of Figure 1.

Figure 4 is a front sectional view of a second embodiment of the invention.

Figure 5 is a right side sectional view of the second embodiment along line 5-5 of Figure 4.

Figure 6 is a left side sectional view of the second embodiment along line 6-6 of Figure 4.

Figure 7 is a front sectional view of a third embodiment of the invention.

Figure 8 is a right side sectional view of the third embodiment along line 8-8 of Figure 7.

Figure 9 is a top sectional view of the third embodiment along line 9-9 of Figure 8.

Figure 10 is a front sectional view of a fourth embodiment of the invention.

Figure 11 is a side sectional view of the fourth embodiment along line 11-11 of Figure 10.

DETAILED DESCRIPTION OF THE INVENTION

The invention includes articles comprising coatings having shapes selected from spheroids, ellipsoids, cylinders and rectangular prisms in combination with cores having spheroidal, ellipsoidal, cylindrical or rectangular prismatic shapes with the proviso that if the coating and core are both spheroidal or both are cubic they are not concentric.

The invention may be best illustrated with reference to the figures.

A first embodiment of the invention, designated by the numeral 1, is illustrated in Figures 1-3.

As shown in Figure 2, the article comprises an ellipsoidal core 11, comprising a hollow cavity, containing the medication, surrounded by a wall 12 and an ellipsoidal coating 10. The core and coating comprise major axes b - b and a - a and minor axes b' - b' and a' - a', respectively. Other points on the surface of the core and coating are indicated by c and c', respectively.

After the device has been in contact with the eroding fluid for a period of time t_1 the coating will have eroded, uniformly, to points b_1, c_1, and a_1. At a later time t_2 the coating will have eroded completely along major axis b - b thereby exposing the points b' on the core and the surface of the core begins to dissolve thereby releasing the medication into the contacting fluid. Erosion of the coating will continue until, at a time t_3, the surface of the core between points b' and points c' will have become exposed thereby releasing additional medication into the eroding fluid. At that time a portion of the coating between c' and a_3, having a thickness a' - a_3 will remain. During erosion of the coating, after the first release of medication, the exposed surface area of, and thereby the flux from, the core will increase. However, since the concentration of medication in the core will be decreasing, during that time, the release rate will be essentially constant until such a time when too little of the core wall remains and the balance of the medication is immediately released into the fluid.

As the coating erodes it takes the shape of an ellipsoid truncated at both ends. If the core wall comprises a composition soluble in the eroding fluid, the wall of the core will completely dissolve, after a time, and when said wall has dissolved and the area of the openings of the the truncated ellipsoidal core is sufficiently large the balance of contained medication will be released quickly in an uncontrolled manner.

If, however, the core wall is insoluble (e.g., an insoluble, osmotically permeable wall) or the core is a matrix tablet the structure of the core will maintain itself for a longer time, and, in the case of the osmotic tablet, it will not lose its form.

In Figures 1-3, the article illustrated is one wherein the thickness of the coating along the minor axis is less than, and continually increases to, that along the minor axis. It is to be understood that the reverse is also within the scope of the invention, i.e., where the thickness along the major axis is greater than along the minor axis. Furthermore, although the shape of the device along the minor axis, as shown in Figures 1-3, is circular it can also be ellipsoidal, rectangular, square, etc.

The composition of the coating will be chosen, as required, to be erodible by any one, or more, of the fluids in the esophagus, stomach and intestine.

If the coating is erodible by the esophageal fluids and it is desired that the contained medication not be released except in the stomach or intestine, the minimum coating thickness will be chosen so that sufficient coating remains on the core to prevent release of the medication until the article passes through the esophagus. The

article then passes into the stomach where the surface coating begins, or continues if erosion had commenced in the esophagus, to erode if the coating is sensitive to the acidic stomach fluids. If the coating is, instead, sensitive to the basic intestinal fluids the article will pass from the stomach into the intestine where erosion will continue or commence. In some cases, erosion of the coating with concomitant release of the medication will occur in the stomach and intestine.

Figures 4-6 illustrate a second embodiment of the invention, comprising a medication containing hollow cylindrical core 13 comprising a water insoluble, water permeable plastic wall 17, partially covered, at its end portions, by a cylindrical coating having non-uniform thicknesses. As shown in Figure 4, the central portion 16 of the wall 17 of the core 13 is uncoated. The left portion of the coating comprises a longitudinal section 14, adjacent the uncoated portion 16 of the core wall 17, and a transverse end section 20 of unequal thicknesses. The right portion of the coating comprises a transverse end section 21 and a longitudinal section 15 disposed between the uncoated section 16 of the core surface and said end sections.

In Figures 4-6 the thicknesses of all of the coating sections 14, 15, 20 and 21 are shown to be unequal. The thicknesses of the coating sections increase according to the order: is $15 < 14 < 21 < 20$. In the practice of the invention it is only necessary that two of the coating sections 14, 15, 20 and 21 be of unequal thickness.

After being placed in the eroding fluid the medication is first released through the uncoated portion 16 of the core wall 17. After a period of time, the coating section 15 will have eroded completely thereby exposing additional surface on the core. The resultant increased surface area of the exposed portion of the core will result in an increased drug release rate. After an additional period of time, the coating section 14 will have completely eroded, the total exposed surface area will have again increased and the release rate of the medication will also have increased again. The above will continue until coating section 21 and then section 20 will have completely eroded. With proper choice of coating composition and thicknesses, core wall composition and medication concentration various combinations of release rate and time for complete release can be achieved.

A first aspect of a third embodiment of the invention comprising a circular cylindrical core 22 and a rectangular prismatic matrix coating 27 is illustrated in Figures 7-9. As shown in Figures 8-9 all six of the coating sections, i.e., sections 23, 24, 25,

26, 27 and 28, are of unequal thicknesses. This embodiment functions in the same manner as the first and second embodiments, i.e., as one section of coating is eroded the underlying portion of the core is exposed to the eroding fluid thereby permitting the medication to be released with concomitant reduction of the concentration of the medication in the tablet. As a result of the increasing exposed surface area and decreasing medication concentration in the core, the medication is released into the fluid at a sustained and approximately constant rate. Thus, by proper choice of coating composition, coating thicknesses, matrix binder composition and medication concentration in the tablet articles having differing drug release rates and times for total medication release may be prepared.

In a second aspect of the third embodiment, illustrated in Figures 10 and 11, the coating 29 comprises an ellipsoid and the core 30 a cylinder. This article functions in a similar manner to that of the first aspect of this embodiment.

The core can be of any type known in the art including soluble capsules, such as gelatin, porous capsules made of materials such as cellulose acetate and matrix tablets. The specific core type will be selected by the user in accordance with his requirements, e.g., compatibility with the medication.

The thickness and composition of the coating will be so chosen that erosion will occur, as required, in the esophagus, stomach or intestine or any combination thereof.

The coating composition comprises substances which are selectively, but readily soluble in, or disintegratable by, the stomach fluids or intestinal fluids. If it is intended that the medicament be released in the stomach, the coating composition must be one that will be removed by the acid fluids of the stomach. On the other hand, if it is intended that the medicament be released in the intestines (i.e. the article is to pass through the stomach substantially intact) the coating composition must be acid resistant and one that will be removed under the alkaline condition of the intestines.

For removal in the stomach, suitable coating compositions are polyvinyl pyrrolidone and solid polyethylene glycols, poly (ortho ester), poly (ϵ-caprolactone), poly (acrylic acid), poly (vinyl alcohol), hydroxypropylmethyl cellulose, dextran, gelatin, polyacrylamide, polysaccharides, gum arabic, polyphosphates, Eudragit (trademark) E100 (a copolymer of dimethylaminoethyl methacrylate and methacrylic acid ester), a copolymer of glutamic acid and ethyl glutamate, polyglycolic acid, polylactic acid, a copolymer of lactide and ϵ-caprolactone and a terpolymer of lactide, glycolide and

ε- caprolactone. For removal in the intestines, suitable coating compositions include cellulose acetate phthalate, hydroxypropylmethylcellulose acetate succinate, hydroxypropyl-methylcellulose phthalate and Eudragit (trademark) L 100 (a copolymer of methacrylic acid and methacrylic acid ester).

The desired rate of erosion may sometimes be achieved by a combination of materials from both groups.

The coating composition is applied to the tablet or capsule core, the thickness being dependent upon the desired rate of release of the medication from the tablet. In practice, the range of thickness of the coating may be varied in accordance with the medicament employed and the amount of control of release desired by the practitioner hereof.

To apply the coating composition, conventional tablet coating practices are used. They include use of a tumbling barrel, for the dose forms, into which the coating composition is sprayed or fluidized column techniques in which the coating composition is sprayed upwardly through the bed of dose forms.

Heretofore, it has been the practice to apply an enteric type coating to pharmaceutical tablets to insure non-lesion inducing passage through the stomach. This enteric-type coating resists disintegration by stomach fluids but is fully disintegrated or dissolved by the intestinal fluids during its passage through the intestine. The present invention normally obviates the necessity for any such enteric-type coating. That is because the coating only dissolves slowly, if at all, in the stomach fluids and prevents or delays release of the medicinal agent in the stomach in accordance with the user's requirements. It allows slow release of the medicinal agent from the tablet into either the stomach or the intestines, depending on the user's needs.

The coating of the invention not only restricts the access of the gastro-intestinal fluids to the medicinal agent of the matrix core, but it moreover serves to position or space the medicinal agent itself away from the gastro-intestinal mucosa so that a large concentration thereof is not permitted to reach a comparatively small area of the gastro-intestinal mucosa.

In the practice of this invention, it is possible to provide a final overcoating to improve the appearance, taste or stability of the tablet. They may contain sugar, or a film former in combination with dyes or pigments, or even other medicaments. This

latter medicament may, for example, be one which is to be administered with the drug in the tablet core but which should not be in contact with each other in the complete tablet. This may be because of the incompatibility of the two or because it is desired that the medicine in the outer coating be released rapidly and that the drug in the core be released slowly.

The following examples are illustrative of the present invention and are not to be construed as limiting.

EXAMPLE 1

SOFT GELATIN CAPSULE WITH A NON-UNIFORM ERODIBLE COATING

Soft gelatin capsules (#6 oblong) of Procardia® (10 mg nifedipine) were coated with hydroxypropylmethylcellulose acetate succinate in a Hi-Coater (trademark). The coating level was thinner at the two ends of the capsule as illustrated in Figure 1. The coated and uncoated capsules were placed in a USP dissolution apparatus containing simulated intestinal fluid (U.S.P. XXII test solution adjusted to pH 7.0) at 37°C and stirred at 50 rpm. Aliquots of the test fluid were removed, from the apparatus, periodically and assayed for released medication at 225 nm in a UV spectrophotometer.

The in vitro release of nifedipine at pH 7.0 was monitored at 225 nm using a UV spectrophotometer. The erosion of the capsules in water started at the ends of the capsule where the coating was thinner. The in vitro release profile as shown in Figure 5 was fairly linear over 6 hours. For uncoated Procardia® capsules, nifedipine was released at pH 7.0 in 2 hours.

As shown in Table I the coated capsules released the medication at an approximately constant rate over a period of about six hours. On the other hand, more than half of the contained medication was released from the uncoated capsules within the first hour and the balance within the second hour.

TABLE I

TIME (HOURS)	% NIFEDIPINE RELEASED FROM UNCOATED CAPSULE	% NIFEDIPINE RELEASED FROM COATED CAPSULE
0	0.0	0.0
0.5	4.6	4.6
1.0	61	4.6
2.0	100	17.8
4.0	100	50.8
6.0	100	100
8.0	100	100

EXAMPLE 2

OSMOTIC CAPSULE WITH A NON-UNIFORM ERODIBLE COATING

Pseudoephedrine HCl (210 mg) was placed in a capsule made of a porous cellulose acetate membrane. The capsule was coated with 10 mg Eudragit (trademark) L100 at one end and 20 mg at the other, leaving the center of the capsule uncoated. This is illustrated in Figure 2.

The coated and uncoated capsules were placed in a USP dissolution apparatus containing simulated gastric fluid (U.S.P. XXII test solution, without enzyme, adjusted to pH 2.0) at 37°C and stirred at 50 rpm. Aliquots of the test fluid were removed, from the apparatus, periodically and assayed for released medication by HPLC using a Nova - Pak (trademark) C 18 column at a 254 nm detection wavelength.

Table II shows that very little of the medication was released by the coated capsules during the first three hours after exposure to the simulated gastric fluid. About one fourth of the medication was released during the next hour after which the medication was released at a sustained rate whereby only about 80% of the contained medication was released after a total exposure time of about fifteen hours. On the other hand, the uncoated capsules rapidly released their contained medication with about a third of the medication being released in the first two hours after exposure to the test fluid. The uncoated capsules then released the balance of their contained medication at a sustained rate which was greater than that for the coated capsules. As a

consequence, most of the medication had been released from the uncoated capsules in about ten hours.

TABLE II

TIME (HOURS)	% PSEUDOEPHEDRINE HCl RELEASED FROM UNCOATED OSMOTIC CAPSULE	% PSEUDOEPHEDRINE HCl RELEASED FROM COATED OSMOTIC CAPSULE
0	0	0
1	11.3	-
2	35.0	1.6
3	51.1	5.2
4	61.2	27.8
5	72.7	36.1
6	80.1	45.5
7	88.8	51.9
8	91.4	58.3
9	92.9	63.0
10	94.0	66.6
11		70.4
12		73.1
13		75.5
14		77.2
15		78.7

EXAMPLE 3

MATRIX TABLET WITH A NON-UNIFORM ERODIBLE COATING

Matrix tablets comprising flat faced circular discs of 5/8 inch diameter and 1/8 inch thickness were prepared comprising the following composition:

Ingredients	mg/tablet
Acrylic acid copolymer	330
Lactose	100
Pseudoephedrine HCl	120
Magnesium Stearate	11
Total	561

The tablet was annealed at 110°C for 10 minutes to become nondisintegrating in water at pH 2.0. The tablet was coated with an erodible polymer, Eudragit (trademark) L30D (a copolymer of methacrylic acid and methacrylic acid esters), at different levels on each side. For example, 6.9 mg and 13.8 mg on flat surfaces of the tablet and 1.9 mg on the edge side of the tablet. This is illustrated in Figure 3. The tablet was placed in stirred water (pH 2.0) at 37°C. The in vitro release profile as shown in Figure 7 was fairly linear over 14 hours.

The coated and uncoated tablets were placed in the a USP dissolution apparatus containing simulated gastric fluid (U.S.P. XXII test solution, absent enzyme, adjusted to pH 2.0) at 37°C and stirred at 50 rpm. Aliquots of the test fluid were removed, from the apparatus, periodically and assayed for released medication by HPLC using a Nova - Pak C 18 column at a 254 nm detection wavelength.

Table III shows that very little of the medication was released by the coated tablets within the first hour after exposure to the simulated gastric fluid whereas about one third of the medication will have been released from the uncoated tablets during that time. The coated tablets then continued to release the medication at a sustained, approximately constant rate during the next fourteen hours. At that end of that time only about 60% of the contained medication had been released. On the other hand, after the initial rapid release of medication the uncoated capsules had released the medication at a sustained non-constant rate which was greater than that of the coated tablets. As a consequence, about 86% of the medication originally contained in the uncoated tablets was released within ten hours.

TABLE III

TIME (HOURS)	% PSEUDOEPHEDRINE HCl RELEASED FROM UNCOATED DISK SHAPED MATRIX TABLET	% PSEUDOEPHEDRINE HCl RELEASED FROM COATED DISK SHAPED MATRIX TABLET
0	0	0
1	34.9	4.4
2	52.3	8.6
3	61.9	13.3
4	71.0	18.1
5	76.5	23.0
6	79.3	29.6
7	80.0	33.0
8	85.2	38.4
9	83.4	45.5
10	86.1	45.5
11		48.9
12		51.5
13		54.3
14		56.9
15		59.7

EXAMPLE 4

MATRIX TABLET WITH A NON-UNIFORM ERODIBLE COATING

The tablet composition of Example 3 was compressed into oblong shaped tablets. These tablets were then annealed at 100°C for 10 minutes to become non-disintegrating in water at pH 2.0. The tablets were then coated with 2% (w/w) Eudragit (trademark) L100, in a Hi Coater (trademark). Because of the shape of the tablets, a coating of non-uniform thickness was obtained as illustrated in Figure 4. The tablet was placed in stirred water (pH 2.0) at 37°C. The in vitro release profile as shown in Figure 8 was fairly linear over 12 hours.

The coated tablets and their controls were treated as in Example 3. As shown in Table IV, after about one hour of exposure to the test fluid the coated tablets released their contained medication at a sustained, approximately constant rate with only about 64% of the medication being released in at about twelve hours. On the other hand, the uncoated tablets released about one-third of their contained medication within the first hour of exposure. The balance of the contained medication was released at a slower but non-constant rate with almost all of the medication having been released within twelve hours.

TABLE IV

TIME (HOURS)	% PSEUDOEPHEDRINE HCl RELEASED FROM UNCOATED OBLONG SHAPED MATRIX TABLET	% PSEUDOEPHEDRINE HCl RELEASED FROM COATED OBLONG SHAPED MATRIX TABLET
0	0	0
1	30.1	2.1
2	47.5	9.8
3	58.6	17.1
4	67.4	25.0
5	75.3	31.7
6	79.9	37.8
7	86.2	43.7
8	89.6	48.8
9	92.5	53.3
10	93.3	56.2
11	95.3	60.3
12	96.4	63.8

Although specific forms and types of articles have been illustrated it is to be understood that combinations of all types and forms known to the art may be used in preparing the articles of the invention.

Furthermore, it is to be understood that the above proposed theory of operation of the devices of the invention is not a part of the invention.

CLAIMS

1. An improved article for the sustained release of pharmaceuticals comprising a core, containing said pharmaceuticals, at least a part of which is coated with an erodible coating wherein the improvement comprises that the thickness of said coating on said core is not constant.

2. The method of claim 1 wherein the shape of said coating is spheroidal and the shape of the core is selected from the group consisting of ellipsoidal, cylindrical, rectangular prismatic and spheroidal shapes with the proviso that if the coating and core both comprise spheroidal shapes they are not concentric .

3. The article of claim 1 wherein the shape of said coating is ellipsoidal and the shape of the core is selected from the group consisting of ellipsoidal, cylindrical, rectangular prismatic and spheroidal shapes.

4. The article of claim 1 wherein the shape of said coating is cylindrical and the shape of the core is selected from the group consisting of ellipsoidal, cylindrical, rectangular prismatic and spheroidal shapes.

5. The article of claim 1 wherein the shape of said coating is that of a rectangular prism and the shape of the core is selected from the group consisting of ellipsoidal, cylindrical, rectangular prismatic and spheroidal shapes with the proviso that if the coating and core are both cubic they are not concentric .

6. The article of claim 1 wherein said coating is erodible by stomach fluids.

7. The article of claim 1 wherein said coating is resistant to stomach fluids and erodible by intestinal fluids.

8. The article of claim 6 wherein said coating comprises a composition selected from the group consisting of polyvinyl pyrrolidone, solid polyethylene glycols, poly (ortho esters), poly (ϵ-caprolactone), poly (acrylic acid), poly (vinyl alcohol), hydroxypropylmethyl cellulose, dextran, gelatin, polyacrylamide, polysaccharides, gum arabic, polyphosphates, copolymers of dimethylaminoethyl methacrylate and methacrylic acid esters, coplymers of glutamic acid and ethyl glutamate, polyglycolic acid, polylactic acid, coplymers of lactide and ϵ-caprolactone and terpolymers of lactide, glycolide and ϵ-caprolactone.

9. The article of claim 7 wherein said coating comprises a composition selected from the group consisting of cellulose acetate phthalate, hydroxypropylmethyl-

cellulose acetate succinate, hydroxypropyl-methylcellulose phthalate and copolymers of methacrylic acid and methacrylic acid esters.

10. The article of claim 1 wherein the core is selected from the group consisting of water soluble capsules, water insoluble porous capsules and matrix tablets.

11. An improved method for preparing articles for the controlled sustained release of orally administrable pharmaceuticals comprising a core, containing said pharmaceuticals, at least part of which is coated with an erodible coating wherein the improvement consists of applying a non-uniform thickness of coating to the core.

12. The method of claim 11 wherein said core is selected from the group comprising water soluble capsules, porous water-insoluble plastic osmotic capsules and matrix tablets.

13. The method of claim 11 wherein the shape of said coating is spheroidal and the shape of the core is selected from the group consisting of ellipsoidal, cylindrical, rectangular prismatic and spheroidal shapes with the proviso that if the coating and core both comprise spheroidal shapes they are not concentric .

14. The method of claim 11 wherein the shape of said coating is ellipsoidal and the shape of the core is selected from the group consisting of ellipsoidal, cylindrical, rectangular prismatic and spheroidal shapes.

15. The method of claim 11 wherein the shape of said coating is cylindrical and the shape of the core is selected from the group consisting of ellipsoidal, cylindrical, rectangular prismatic and spheroidal shapes.

16. The method of claim 11 wherein the shape of said coating is that of a rectangular prism and the shape of the core is selected from the group consisting of ellipsoidal, cylindrical, rectangular prismatic and spheroidal shapes with the proviso that if the coating and core are both cubic they are not concentric .

17. The method of claim 12 wherein said coating comprises a rectangular prism and said core comprises a cylindrical matrix tablet.

18. The method of claim 12 wherein said coating comprises an ellipsoid and said core is a cylindrical matrix tablet wherein said matrix is insoluble in aqueous body fluids.

19. The method of claim 12 wherein said coating comprises an ellipsoid and said core is a drug containing ellipsoidal capsule soluble in aqueous body fluids.

20. The method of claim 12 wherein said coating comprises a cylinder covering only part of the core which comprises a cylindrical osmotic capsule comprising a coating insoluble in, and permeable to, aqueous body fluids.

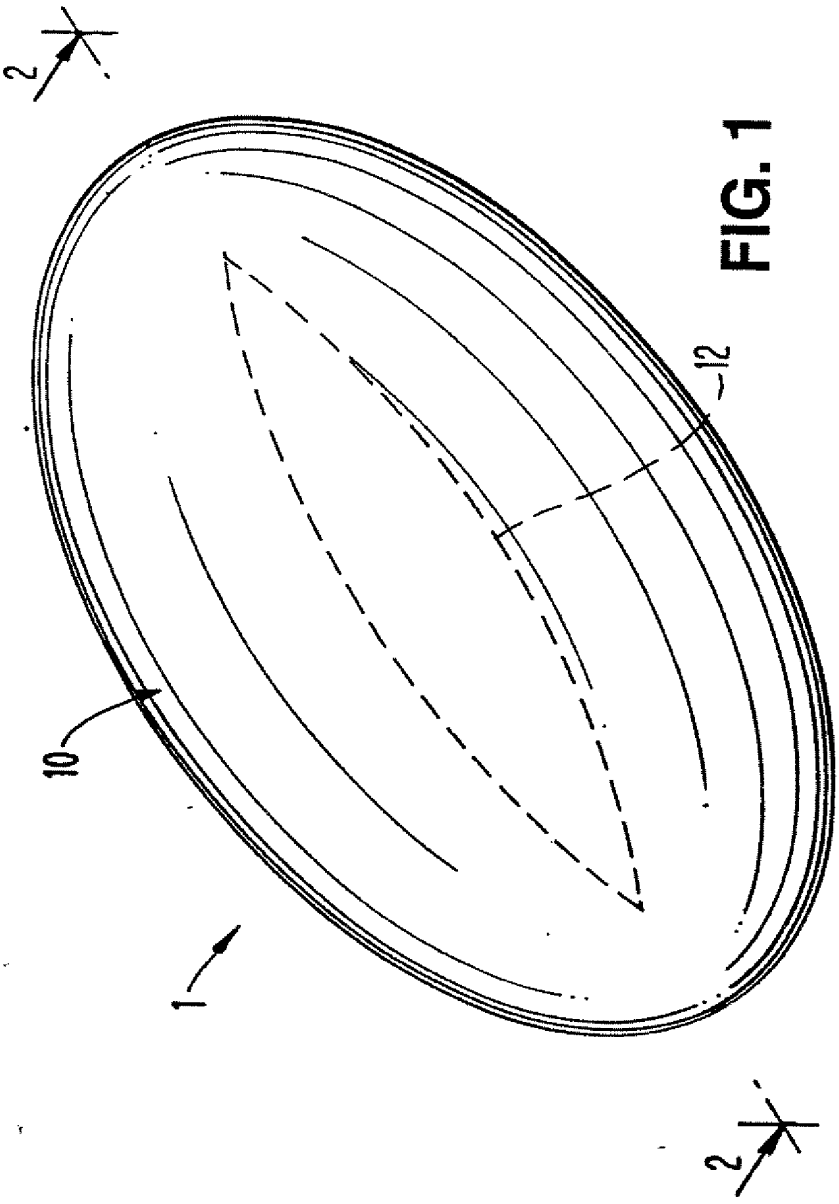


FIG. 1

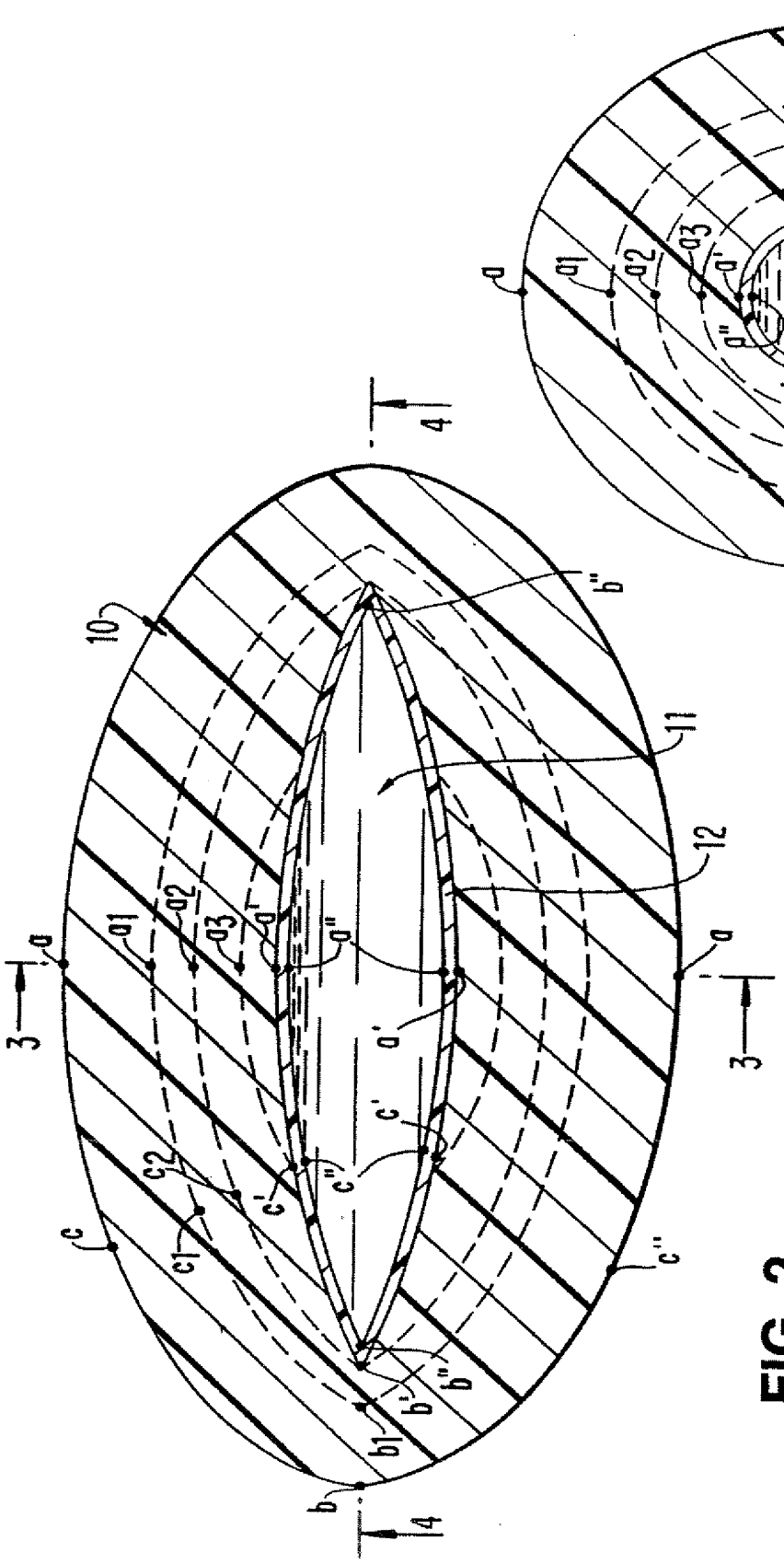


FIG. 2

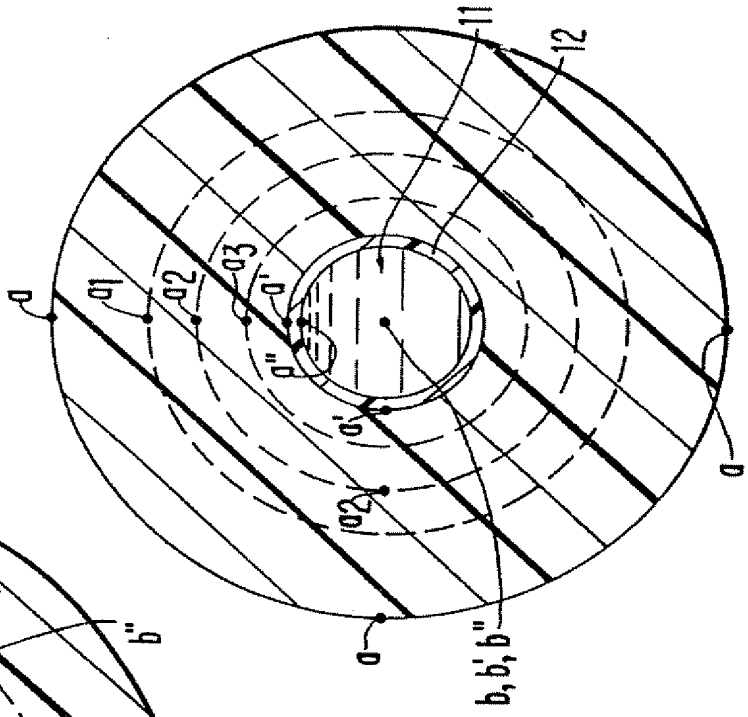


FIG. 3

FIG. 4

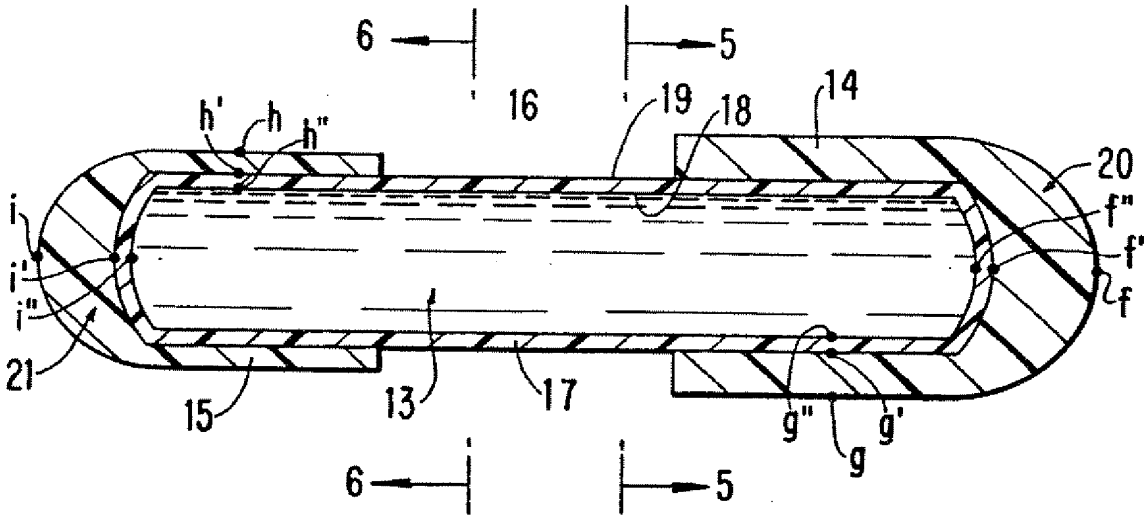


FIG. 5

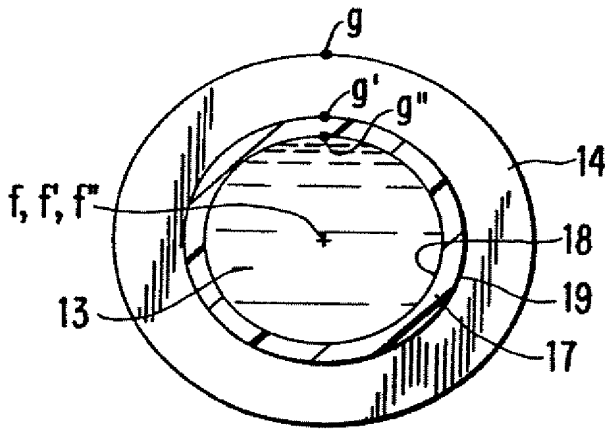


FIG. 6

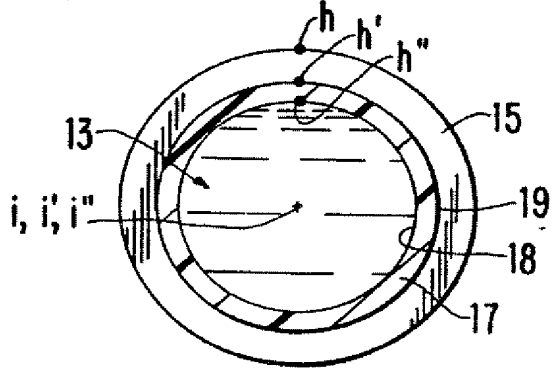


FIG. 7

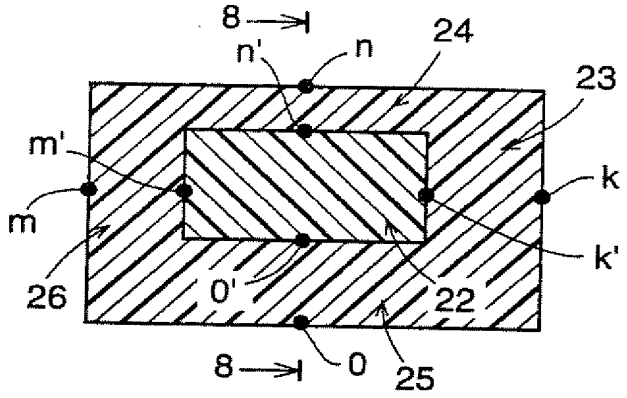


FIG. 8

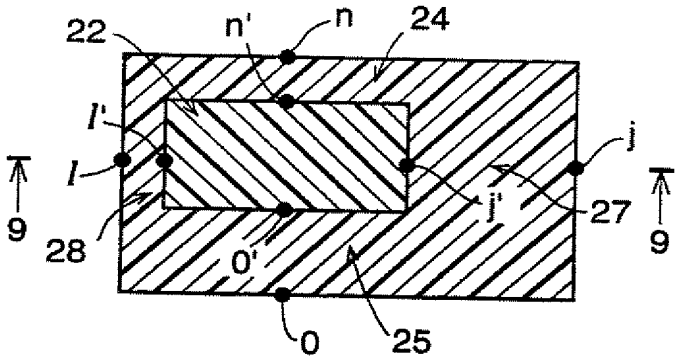


FIG. 9

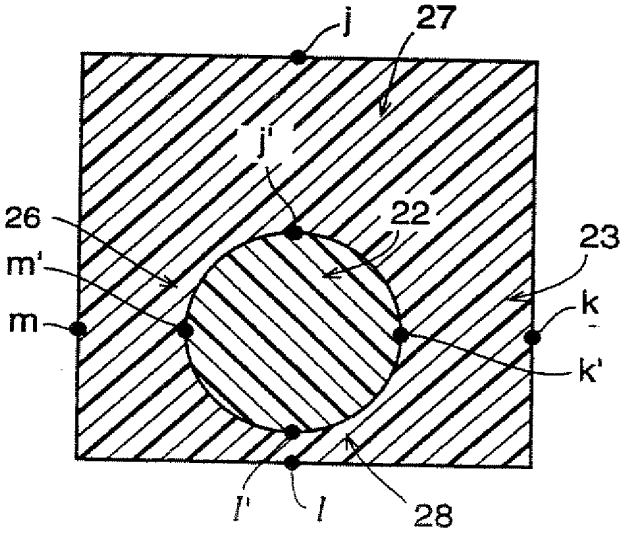


FIG. 10

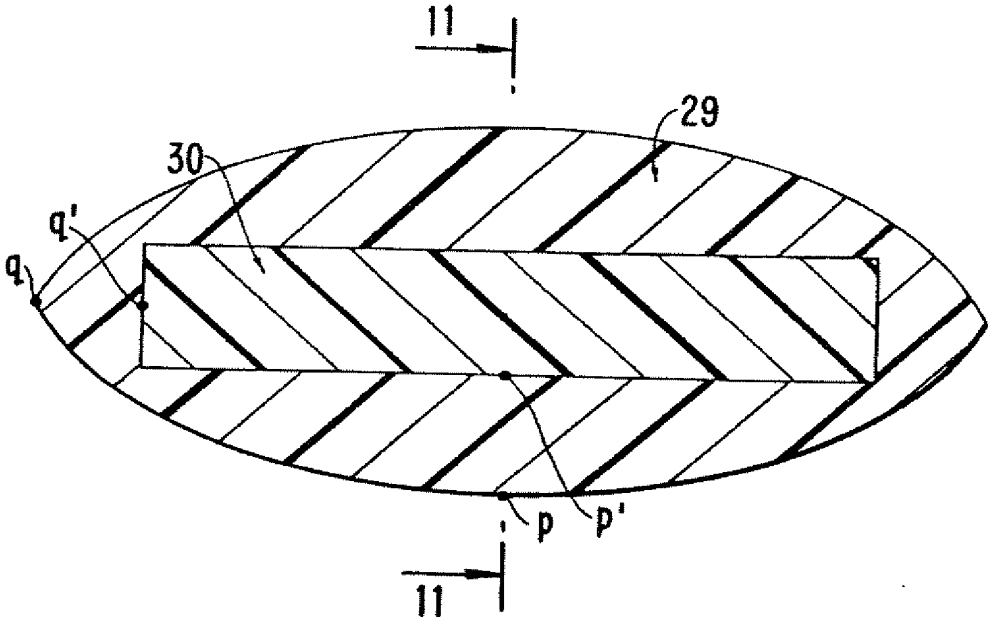
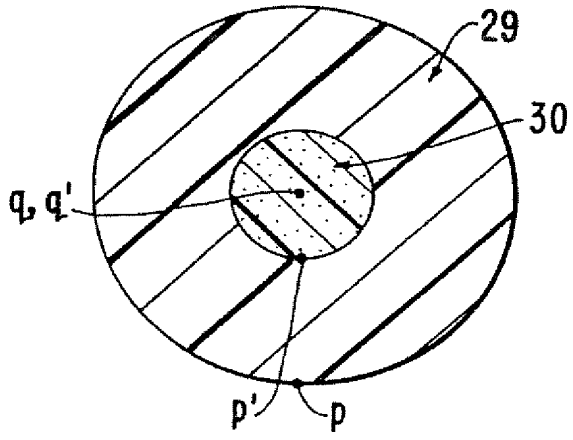


FIG. 11



INTERNATIONAL SEARCH REPORT

International Application No PCT/US 93/06447

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K9/20; A61K9/28; A61K9/48

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	GB,A,994 742 (THE WELLCOME FOUNDATION LIMITED) 10 June 1965 see figure 2 see claims 4-6 see page 3, line 9 - line 16	1-20
X	US,A,3 015 610 (ROY Y. SANDERS) 2 January 1962 see figure 2 see column 2, line 40 - line 54	1-20
X	FR,A,1 603 314 (ETABLISSEMENTS WANDER) 5 April 1971 see figure 2 see page 2, line 25 - line 33	1-20

-/--

° Special categories of cited documents :[10]

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
05 OCTOBER 1993	14. 10. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	VENTURA AMAT A.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	EP,A,0 259 219 (UNIVERSITE DE MONTREAL) 9 March 1988 see figure 2A see claim 1 see page 3, line 15 - line 22	1-20

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9306447
SA 76905

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A-994742		None	
US-A-3015610		FR-A- 1259997 GB-A- 897141 NL-C- 102235 NL-A- 234514	
FR-A-1603314	05-04-71	None	
EP-A-0259219	09-03-88	US-A- 4816262 JP-A- 63072623	28-03-89 02-04-88

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82